

COMPARISON OF MICROVASCULAR FILTRATION IN HUMAN ARMS WITH AND WITHOUT POSTMASTECTOMY OEDEMA

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SUMMARY

Oedema is caused by impaired lymphatic drainage and/or increased microvascular filtration. To assess a postulated role for the latter in postmastectomy oedema, filtration was studied in the forearms of 14 healthy subjects and 22 patients with chronic, unilateral arm oedema caused by surgical and radiological treatment for breast cancer. A new non-contact optical device (the Perometer) and a conventional mercury strain gauge were used simultaneously to record forearm swelling rates caused by microvascular filtration during applied venous congestion. Filtration rate (FR) per 100 ml tissue was measured over 10–15 min at a venous pressure of 30 cmH₂O, a pressure reached in the dependent forearm (FR₃₀), and then at 60 cmH₂O (FR₆₀). Apparent filtration capacity of 100 ml soft tissue (CFC_a) was calculated from $FR_{60} - FR_{30}/30$, after adjustment for bone volume. The Perometer and strain gauge gave similar results in normal and oedematous arms. Mean CFC_a in healthy subjects was $(3.8 \pm 0.4) \times 10^{-3}$ ml (100 ml)⁻¹ cmH₂O⁻¹ min⁻¹, close to literature values. In the patients, FR₃₀ was 47% lower in the oedematous forearm than in the opposite, unaffected forearm ($P = 0.04$). FR₆₀ showed a similar trend but did not reach significance ($P = 0.15$). The values of CFC_a of $(2.2 \pm 0.5) \times 10^{-3}$ ml (100 ml)⁻¹ cmH₂O⁻¹ min⁻¹ in the oedematous arm and $(2.8 \pm 0.5) \times 10^{-3}$ ml (100 ml)⁻¹ cmH₂O⁻¹ min⁻¹ in the unaffected arm were not significantly different ($P = 0.47$). When differences in arm volume on the two sides were taken into account, the total fluid load on the lymphatic system of the oedematous forearm was $(411.0 \pm 82.2) \times 10^{-3}$ ml min⁻¹ at 30 cmH₂O and $(1168 \pm 235.6) \times 10^{-3}$ ml min⁻¹ at 60 cmH₂O, similar to the normal side, namely $(503.7 \pm 109.3) \times 10^{-3}$ ml min⁻¹ and $(1063 \pm 152.0) \times 10^{-3}$ ml min⁻¹, respectively ($P \geq 0.50$). The filtration capacity of the entire oedematous forearm (CFC_a scaled up by total soft tissue volume), $(25.4 \pm 6.2) \times 10^{-3}$ ml cmH₂O⁻¹ min⁻¹, was not significantly greater than that of the normal forearm, $(18.3 \pm 2.6) \times 10^{-3}$ ml cmH₂O⁻¹ min⁻¹ ($P = 0.40$). The results indicate that no major change occurs in the microvascular hydraulic permeability–area product of the forearm, or in the total filtration load on the lymph drainage system during dependency, in the arm with postmastectomy oedema compared with the normal arm. This argues against a significant haemodynamic contribution to postmastectomy oedema.

INTRODUCTION

Oedema develops when there is a prolonged period of imbalance between microvascular filtration rate (filtration from capillaries and venules) and lymphatic drainage rate, and attains a steady state if the altered filtration rate and drainage rate attain equality. Oedema of the arm (postmastectomy oedema, PMO) is a common complication of breast cancer treatment despite the trend towards conservative surgery (Kissin *et al.* 1986; Mortimer *et al.* 1996). Interference

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with the axillary lymphatic drainage route by nodal excision and radiotherapy appears to be the primary, obstructive cause of the eventual PMO. However, the long time lag between treatment and onset of PMO and other puzzling pathophysiological features indicate that additional factors complicate a simple, obstructive aetiology.

Particular puzzling features are that, in established PMO, the concentration of plasma protein in the oedema fluid is lower than in the interstitial fluid from the contralateral, normal arm, and that the oedema protein concentration correlates negatively with the degree of swelling, i.e. concentration decreases in proportion to increased arm volume (Bates *et al.* 1993, 1994). This contrasts with the conventional expectation that plasma protein concentration should rise in oedema of lymphatic origin, since impaired lymphatic drainage should reduce the clearance of escaped plasma proteins from the arm. Three possible explanations for these findings have been put forward, namely (i) reduced permeability of the capillary wall to plasma proteins, (ii) proteolysis within the interstitial compartment, and (iii) increased capillary filtration rate (Bates *et al.* 1994; Stanton *et al.* 1996a). This study addresses proposal (iii), which appears to be indirectly supported by evidence of haemodynamic abnormalities in PMO in the literature.

The mechanism underlying proposal (iii) is that plasma protein concentration in interstitial fluid is determined normally by the rate of transendothelial transfer of protein relative to rate of transfer of fluid. At high filtration rates this ratio decreases, due to endothelial sieving ('reflection') of protein molecules, and this creates an inverse relationship between interstitial protein concentration and filtration rate (Michel, 1984; Taylor & Granger, 1984). The possibility that filtration rate might be increased, secondary to reduced precapillary resistance, stems from previously published reports of hyperaemia in PMO (Jacobsson, 1967; Svensson *et al.* 1994). However, while this could explain reduced interstitial protein concentration, it would create an obvious problem, namely that in the steady state the lymph flow would be raised. This is, at least on initial considerations, contrary to expectation if the axillary lymphatic outflow route has suffered iatrogenic damage. Information on microvascular filtration rates and tissue filtration capacity is thus required to test proposal (iii), as well as to assess whether the fluid load on the damaged lymphatic system is increased, unchanged or decreased.

Microvascular filtration rate (FR) depends on endothelial hydraulic conductance (L_p), area (A) and the Starling pressures, i.e. $FR = L_p A [(P_c - P_i) - \sigma(\pi_p - \pi_i)]$, where P_c is average microvascular blood pressure, P_i is interstitial fluid pressure, σ is the protein osmotic reflection coefficient, and π_p and π_i are the colloid osmotic pressures of plasma and interstitial fluid, respectively (Michel, 1984). P_c is unknown in PMO, but the sum of the Starling pressures opposing filtration, $P_i + \sigma(\pi_p - \pi_i)$, is increased in arms with PMO relative to contralateral arms (Bates *et al.* 1994). There is a modest increase in blood capillary numbers in forearm skin in PMO due to angiogenesis (Roberts *et al.* 1994), which might raise the product $L_p A$, thereby increasing the total fluid load on the lymphatic system. However, this would not in itself reduce the interstitial protein concentration unless the L_p of new vessels was higher than normal. The stimulus to angiogenesis in PMO is unknown, but it is interesting to note that the widespread angiogenic factor VEGF (vascular endothelial growth factor) increases L_p both acutely and chronically (Bates & Curry, 1997; Bates, 1998). Information on the filtration capacity (sum of capillary and venular $L_p A$ products) would thus be of interest.

The primary objectives of the present study were to measure microvascular filtration rates and microvascular filtration capacity in arms with PMO and in contralateral normal arms. Venous occlusion plethysmography (VOP) was used to record the slow swelling of the forearm soft tissue, representing filtration rate, at two venous congesting pressures. Capillary filtration

capacity (CFC) was conventionally assessed from the increase in filtration rate per unit increase in venous pressure.

A secondary purely technical objective was to compare a newer system for recording swelling rates, the Perometer, with the conventional mercury strain gauge method (Michel & Moyses, 1985; Gamble *et al.* 1993). A possible limitation of strain gauge plethysmography is that the mercury loop, which is under tension around the limb, may compress the tissue (especially oedematous tissue) beneath it. This might result in an underestimation of swelling rates. With the optoelectronic volumeter (Perometer), however, limb volume is computed from the interruption of light beams by the arm (Fischbach *et al.* 1986). No compression of tissue occurs, offering a theoretical advantage in the study of PMO. The comparative assessment of the Perometer was made in healthy subjects as well as in patients.

METHODS

Subjects

Twenty-two women (aged 46–85 years; mean, 66 years) with unilateral PMO following breast cancer treatment were recruited from the Lymphoedema Clinic, The Royal Marsden NHS Trust, London and Surrey. The right arm was affected in 13 patients and the left arm in nine. An elastic compression sleeve was worn during the daytime by all patients and the oedema was considered stable. The median interval between completion of radiotherapy and onset of oedema was 18 months (mean 42 months) and the range 0–24 years. The median duration of oedema at the time of study was 5 years (mean 9 years), with a range of 1.25–40 years. Fourteen healthy subjects, eight male and six female (aged 18–49 years; mean, 25 years), were recruited from the student and staff population at St George's Hospital Medical School. No subject had cardiovascular disease or was taking cardiovascular drugs. Caffeine-containing drinks were avoided for 3 h beforehand. The one subject from each group who smoked had not done so since the previous day.

The unaffected arm of each patient provided a paired control for comparison with the arm with PMO. The healthy group was used for comparison of the Perometer with the strain gauge and to provide a value for filtration capacity in normal arms. No attempt was made, therefore, to age- and sex-match the two groups of subjects.

Local Ethics Committee approval was obtained and informed consent given.

Equipment and preparation

This was described in detail previously (Stanton *et al.* 1997, 1998). Briefly, a mercury strain gauge (Lectromed, St Peter, Jersey) was secured around the mid-forearm. The loop, under minimal tension, ran over a series of thin plastic strips, which spread the load to minimize any sinking of the gauge into the tissues. The forearm was inserted horizontally into the measuring frame of the Perometer (300 S, Pero-System, Wuppertal, Germany) and supported. The region measured by the Perometer was a 3.1 mm wide segment located 3 cm proximal to the strain gauge. Previous technical evaluations have confirmed the Perometer's accuracy and reproducibility for static measurement of limb volume and for measurement of the rapid, initial venous swelling during venous congestion (Stanton *et al.* 1997, 1998). Both devices provide a continuous record of circumference *versus* time, from which the percentage swelling rate is calculated, i.e. increase in volume per 100 ml forearm tissue per minute. A minor disadvantage of the Perometer during the prolonged measurements of slow swelling rates was that the software recording file saturated at 1000 s (16.7 min), so it was often necessary to start a fresh computer file in mid-experiment.

A blood pressure cuff (Accoson, London) enclosed in a non-expandable plastic sleeve was wrapped around the upper arm and connected to an inflation unit with compressor (Jun-Air, Nørresundby, Denmark) to generate venous congestion. The congesting pressure in the cuff was recorded by a SensoNor 840 pressure transducer and PM-1000 CWE amplifier (Linton Instrumentation, Diss, Norfolk). Direct measurements show that venous pressure closely mirrors cuff pressure (Levick & Michel, 1978; Christ *et al.* 1997).

In both arms of five patients a photoplethysmograph (PPG) probe (Medasonics, Mountain View, CA, USA) was attached to the skin 3 cm distal to the strain gauge. The probe emits infra-red light into the skin, and the back-scattered light is processed to provide a continuous, semiquantitative record of local cutaneous blood volume. This technique was used to make an independent assessment of the marked oscillations that had been noted in the late-phase circumference record of some subjects, and are thought to be possibly of vascular origin.

Brachial artery pressure was measured by conventional sphygmomanometry. Mean blood pressure and heart rate were recorded during the experiment using a Finapres 2300 (Ohmeda, Louisville, CO, USA). Perometer recordings were saved on computer disk and other parameters were recorded on a six-channel chart recorder (SE400, Servogor, Goerz, Vienna, Austria).

Protocol

The compression sleeve (normally worn during daytime) was removed at least 12 h prior to the commencement of the study. Brachial artery blood pressure was measured. After a 30 min acclimatization period (ambient temperature 25.7–27.5 °C, humidity 29–58%), with the subject relaxed and comfortable, each forearm volume between wrist and olecranon process was measured with the Perometer (Stanton *et al.* 1997). The Finapres cuff was attached to the middle finger of the hand opposite to the side being studied. The mercury strain gauge was calibrated on the arm. With the forearm supported in a horizontal position 5–8 cm below mid-right atrial level, the collecting cuff pressure was inflated quickly to 30 cmH₂O (22 mmHg) and maintained at this pressure for 10–15 min while the swelling (filtration) rate was recorded. Congestion pressure was then increased to 60 cmH₂O (44 mmHg) and swelling rate recorded for a further 10–15 min, followed by deflation. Both arms were studied during the same laboratory visit, the order being alternated for successive subjects.

Measurement of swelling rates and adjustment for bone content

Swelling rate was calculated from the gradual upward slope of the circumference recording from 3 min after venous congestion onwards. The initial steep slope at less than 3 min is caused principally by venous distension, reflecting arterial inflow, whereas the subsequent phase is caused by the accumulation of interstitial fluid and reflects microvascular filtration rate (Krogh *et al.* 1932; Sejresen *et al.* 1981; Michel & Moyses, 1987; Gamble *et al.* 1993). The slope was fitted by an independent operator by eye, the operator being blind to the identity of the limb. Swelling rates were calculated from the slopes as described previously (Stanton *et al.* 1997, 1998).

Results are presented as swelling rate per unit volume of soft tissue rather than per unit volume of arm, an adjustment being made for bone because bone does not swell. The radius and ulna account for 13% of normal forearm volume (Cooper *et al.* 1955), and it was assumed that bone volume on the swollen side was the same as on the normal side.

The change in FR per unit increase in venous pressure per 100 ml tissue is often called capillary filtration capacity, 'capillary' in this context encompassing all microvascular exchange vessels, including venules. The qualification, apparent capillary filtration capacity (CFC_a) is used here because only the increase in venous pressure was known, not that in capillaries (or venules). Nevertheless, true CFC and CFC_a are usually closely related, because the pre- to post-capillary resistance ratio is high (Michel & Moyses, 1987).

Statistical analysis

Comparisons within groups were made using Student's paired *t* test. Regression analysis and correlation coefficients were analysed with Microsoft Excel 7.0 software. Differences were considered significant at $P < 0.05$.

RESULTS

Arm volumes and cardiovascular baseline

In the healthy subjects dominant forearm volume including bone (1232 ± 280 ml, mean \pm s.d., $n = 14$) was 3.6% greater than non-dominant forearm volume (1189 ± 263 ml, $P = 0.0003$, Student's paired *t* test). Brachial artery pressure was $118 \pm 6/79 \pm 7$ mmHg

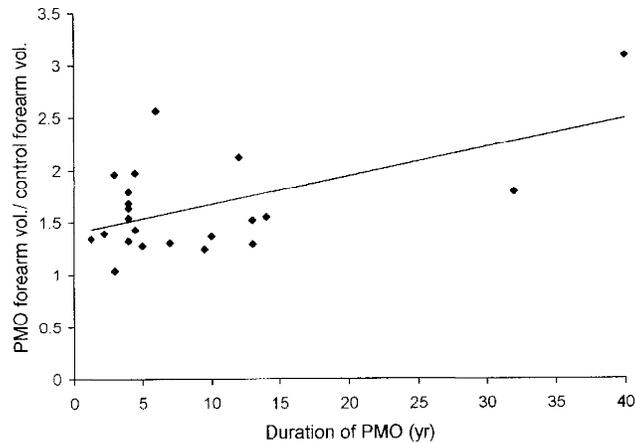


Fig. 1. Scattergram of fractional increase in forearm soft tissue volume *versus* years of duration of postmastectomy oedema (PMO) ($n = 22$). For details of fitted regression line see text.

(systolic/diastolic, mean \pm S.D.), finger arterial pressure 68 ± 11 mmHg (dominant side) and 71 ± 10 mmHg (non-dominant side), heart rate 68 ± 8 min⁻¹, and skin temperatures 33.7 ± 1.7 °C (dominant) and 33.7 ± 1.2 °C (non-dominant). The difference between the brachial artery and finger blood pressure readings (for both groups) is greater than previously reported (Imholz *et al.* 1990), presumably indicating that the subjects were more relaxed for the Finapres measurement.

In the patients, brachial artery pressure was a little higher, $140 \pm 18/88 \pm 9$ mmHg (systolic/diastolic, mean \pm S.D.), reflecting their greater age. Finger arterial pressures were 70 ± 13 mmHg (PMO side) and 72 ± 11 mmHg (unaffected, or control, side, $P = 0.22$), and heart rate 71 ± 9 min⁻¹. Skin temperatures (control 33.3 ± 1.4 °C, PMO 33.4 ± 1.7 °C), provided no indication of cutaneous hyperaemia on the affected side. Forearm volume including bone was 1470 ± 648 ml on the PMO side and 927 ± 230 ml on the control side, a difference of 1.56 ± 0.41 times ($n = 22$, $P = 0.00005$, paired t test). If absolute bone volume is assumed to be the same on the two sides (see Methods), the affected soft tissues had swollen 1.64 ± 0.48 times.

Degree of swelling correlated poorly but significantly with duration of swelling, as shown in Fig. 1 (correlation coefficient $r = 0.55$, $P = 0.008$, $n = 22$). The relative swelling, PMO soft tissue volume/control soft tissue volume ($V_{\text{PMO}}/V_{\text{CTL}}$), was described by the regression equation $V_{\text{PMO}}/V_{\text{CTL}} = 0.027D + 1.396$, where D is duration in years. Therefore forearm soft tissue volume increased on average by 2.7% per year. This result was heavily influenced by two patients with very long-standing, severe swelling. However, in an earlier study of 51 PMO patients the percentage volume increase for the whole arm (wrist to shoulder, including bone) did not correlate significantly with duration (Bates *et al.* 1993).

Volume records during prolonged venous congestion

Perometer records from the arm of a young healthy subject and from an arm with PMO are shown in Fig. 2A and B, demonstrating the slow increase in volume due to prolonged microvascular filtration. In the healthy group, satisfactory, measurable slopes were obtained

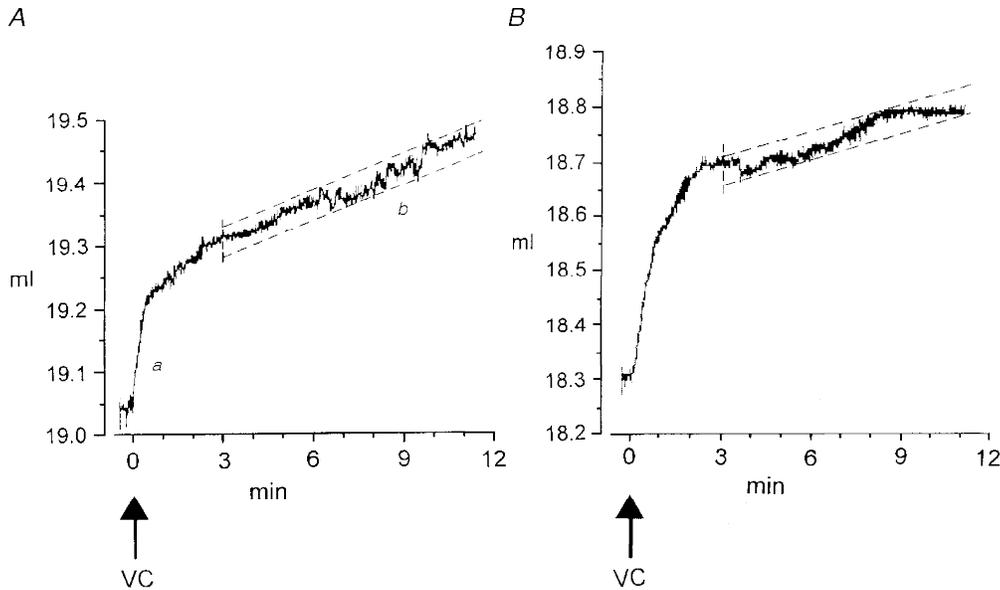


Fig. 2. Perometer recordings of forearm swelling during prolonged venous congestion to 30 cmH₂O. *A*, recording of segment volume in a dominant arm of a healthy subject subjected to 11 min of venous congestion. VC, onset of venous congestion; *a*, phase of rapid venous distension, representing arterial inflow; *b*, phase of slow swelling at > 3 min, representing microvascular filtration into soft tissue interstitium. The measured slope is shown by the dashed lines. *B*, recording from the affected (postmastectomy oedema) arm of a patient. Mild undulation in the recording, as here, was common at the lower congestion pressure. A more pronounced example is shown in Fig. 6.

from 10/14 subjects with the Perometer and 11/14 with the strain gauge. For the patients, however, measurable slopes were obtained from only 5/22 with the Perometer and 10/22 with the strain gauge (Table 1). Discarded recordings were erratic, with no clearly discernible slope. This problem, though little discussed, is neither new (see Krogh *et al.* 1932) nor unique to the Perometer, being present in many strain gauge traces too. The problem was more severe in the patients, even in their unaffected arms, than in the younger, healthy group. Slow undulations of slope were especially common at 30 cmH₂O. In the patients, wave amplitude (measured from the strain gauge record, mean \pm S.D.) was 0.31 ± 0.26 ml (100 ml)⁻¹ in the control arm and 0.39 ± 0.31 ml (100 ml)⁻¹ in the arm with PMO ($P = 0.85$, unpaired *t* test). Wave frequency was 0.20 ± 0.07 cycles min⁻¹ in the control arm (range 0.13–0.33 cycles min⁻¹) and 0.14 ± 0.06 cycles min⁻¹ in the arm with PMO (range 0.06–0.23 cycles min⁻¹; $P = 0.12$). Such waves may arise from slow oscillations in vascular tone (see 'Photoplethysmography', below). The ages of patients from whom acceptable recordings were obtained (67.3 ± 13.6 years, mean \pm S.D.) and their degrees of arm swelling (1317 ± 723 ml, an increase of 1.51 ± 0.49 times) were similar to those of patients in whom recordings were unsatisfactory.

Comparison of methods; strain gauge and Perometer results for same arm

Filtration rates at 30 and 60 cmH₂O congestion pressure (FR₃₀, FR₆₀) and CFC_a determined with the Perometer were not significantly different from those determined simultaneously with the strain gauge. This was the case both in healthy subjects and in patients (see Table 1).

Table 1. Comparison of forearm soft tissue filtration rates (FR_{30} and FR_{60}) and capillary filtration capacity (CFC_a) measured by a Perometer and by a mercury strain gauge during venous congestion

Healthy gp.	Perometer			Mercury strain gauge			P
	Dominant arm	Non-dominant arm	Both arms	Dominant arm	Non-dominant arm	Both arms	
FR_{30}	69.4 ± 14.0 (10)	62.0 ± 9.2 (10)	65.7 ± 8.2 (20)	55.6 ± 10.8 (11)	57.2 ± 14.4 (11)	57.7 ± 7.9 (22)	0.12
FR_{60}	172.2 ± 20.3 (10)	181.8 ± 13.0 (10)	177.0 ± 52.6 (20)	209.4 ± 38.2 (11)	141.9 ± 29.8 (11)	170.7 ± 21.4 (22)	0.74
CFC_a	3.4 ± 0.6 (10)	4.0 ± 0.6 (10)	3.7 ± 0.4 (20)	5.1 ± 1.1 (11)	2.8 ± 0.6 (11)	3.8 ± 0.6 (22)	0.94
Patients:	Control arm	PMO arm		Control arm	PMO arm		
FR_{30}	74.8 ± 27.1 (5)	44.3 ± 14.3 (5)		55.1 ± 11.2 (10)	34.7 ± 4.7 (10)		0.18
FR_{60}	159.8 ± 56.1 (5)	99.1 ± 36.2 (5)		128.3 ± 14.4 (10)	108.9 ± 16.5 (10)		0.91
CFC_a	2.8 ± 1.0 (5)	1.8 ± 1.1 (5)		2.4 ± 0.4 (10)	2.5 ± 0.5 (10)		0.39

FR values are given as (mean ± S.E.M.) × 10⁻³ ml (100 ml)⁻¹ min⁻¹ and CFC_a values are given as (mean ± S.E.M.) × 10⁻³ ml (100 ml)⁻¹ cmH₂O⁻¹ min⁻¹, with the number of measurements in parentheses. For comparison of arms see Table 2. *P* values refer to paired comparisons (Student's *t* test) when the two methods were used simultaneously on the same arm. Measurements by the two methods were obtained simultaneously on both arms of 8 healthy subjects, giving *n* = 16 for the paired comparison. For the patients there are *n* = 8 paired comparisons.

The degree of methodological agreement between individual measurements is analysed further by the method of Bland & Altman (1986) in Fig. 3. The swelling rate measured by the Perometer minus that measured simultaneously by the strain gauge was plotted against their average, the best available measure of the true swelling rate for that forearm. This plot shows that, although the mean results of the two methods are not significantly different (the mean difference is close to zero) and there is no significant relation between the difference and average value (i.e. little overall bias), large differences can nevertheless occur in either direction in individual cases. For 24 arms at 30 cmH₂O, six of the differences lay outside 1 s.d. of the mean difference (Fig. 3A), and at 60 cmH₂O there were 8/24 results outside 1 s.d. (Fig. 3B).

In view of the absence of any consistent difference or bias between the two methods, the two results for a given arm were averaged. This result is used in comparisons between arms except where only one recording was technically satisfactory, when that result was used.

Comparison between arms in healthy subjects

Filtration rates per 100 ml of normal soft tissue are plotted in Fig. 4. Neither the filtration rates nor the filtration capacity were significantly different between the dominant forearm and non-dominant forearm. Means and *P* values for paired comparisons are listed in Table 2. The extrapolated pressure intercept at zero swelling rate, the congestion pressure that needs to be exceeded to induce microvascular filtration, was 10.7 ± 3.1 cmH₂O for the dominant arm and 7.1 ± 5.1 cmH₂O for the non-dominant arm (mean ± S.E.M.). These values did not differ significantly (*P* = 0.56, paired *t* test).

Filtration rate for the soft tissue mass of the entire whole forearm (ΣFR , ml min⁻¹) was calculated as forearm soft tissue volume × FR/100. Since forearm volume was slightly bigger on the dominant side, this accentuated the slight trend towards greater filtration rates on the dominant side. Even so, the difference did not reach statistical significance (*P* = 0.11 at 60 cmH₂O). Aggregate filtration capacity of the forearm (ΣCFC_a), i.e. forearm soft tissue

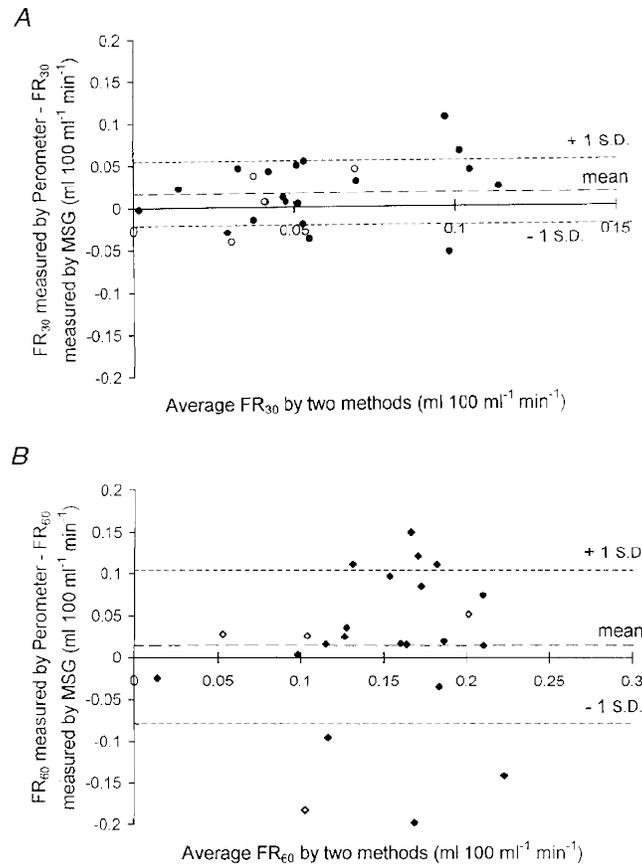


Fig. 3. Comparison of methods. Difference between the filtration rate measured by the Perometer and by the mercury strain gauge (MSG), plotted against the average of the two ($n = 24$). Results are from the healthy group and patients (both arms), with the oedematous arms represented by the open points. The mean difference is shown as a long-dashed line and one standard deviation (s.d.) as short-dashed lines. *A*, filtration rates at 30 cmH₂O congestion pressures (FR₃₀). Mean difference (\pm s.d.) was 0.0167 ± 0.038 ml (100 ml)⁻¹ min⁻¹. *B*, filtration rates at 60 cmH₂O (FR₆₀). Mean difference 0.0139 ± 0.0910 ml (100 ml)⁻¹ min⁻¹.

volume \times CFC_a/100 (ml cmH₂O⁻¹ min⁻¹), was not significantly different on the two sides either (Table 2).

There were thus no major microvascular differences between dominant and non-dominant arms that might bias the comparison of pairs of arms when one of them is affected by oedema.

Comparison between arms in women with unilateral postmastectomy oedema

Filtration rates per 100 ml soft tissue in patients are plotted in Fig. 5A. Filtration rate at 30 cmH₂O was significantly lower in the arm with PMO than in the contralateral arm ($P = 0.04$, paired t test). At 60 cmH₂O the filtration rate per 100 ml was lower in the arm with PMO in 8/11 patients but the differences did not reach statistical significance ($P = 0.15$). The pressure intercept at zero swelling rate was 5.4 ± 6.6 cmH₂O for the control arm and

Table 2. Between-arms comparison of soft tissue filtration rates (FR_{30} and FR_{60}) and capillary filtration capacity (CFC_a)

Healthy group:	Dominant (13)	Non-dominant (13)	Both arms (26)	<i>P</i>
<i>- per 100 ml soft tissue</i>				
FR_{30}	68.0 ± 8.3	57.8 ± 10.3	62.9 ± 6.6	0.50
FR_{60}	199.8 ± 25.8	156.3 ± 19.1	178.1 ± 16.3	0.25
CFC_a	4.4 ± 0.7	3.3 ± 0.4	3.8 ± 0.4	0.24
<i>- whole forearm (soft tissue)</i>				
ΣFR_{30}	726.1 ± 104.2	546.2 ± 75.7	636.1 ± 65.6	0.51
ΣFR_{60}	2126 ± 323	1565 ± 185	1845 ± 191	0.11
ΣCFC_a	46.7 ± 8.9	33.9 ± 5.3	40.3 ± 5.2	0.36
Forearm vol.(ml) (excluding bone)	1056 ± 69	1017 ± 64	1037 ± 55	<0.001
Patients:	Control arm (11)	PMO arm (11)	<i>P</i>	
<i>- per 100 ml soft tissue</i>				
FR_{30}	66.9 ± 12.8	35.5 ± 5.0	0.04	
FR_{60}	149.4 ± 23.9	102.1 ± 13.5	0.15	
CFC_a	2.8 ± 0.5	2.2 ± 0.5	0.47	
<i>- whole forearm (soft tissue)</i>				
ΣFR_{30}	503.7 ± 109.3	411.0 ± 82.2	0.50	
ΣFR_{60}	1063 ± 152.0	1168 ± 235.6	0.77	
ΣCFC_a	18.3 ± 2.6	25.4 ± 6.2	0.40	
Forearm vol. (ml) (excluding bone)	748 ± 65	1202 ± 212	0.03	

FR values are given as (mean ± S.E.M.) × 10⁻³ ml (100 ml)⁻¹ min⁻¹ and CFC_a values are given as (mean ± S.E.M.) × 10⁻³ ml (100 ml)⁻¹ cmH₂O⁻¹ min⁻¹. The number of arm measurements is shown in parentheses. Aggregate values for the entire forearm, ΣFR_{30} and ΣFR_{60} (× 10⁻³ ml min⁻¹) and ΣCFC_a (× 10⁻³ ml cmH₂O⁻¹ min⁻¹) are FR_{30} , FR_{60} and CFC_a , respectively, multiplied by forearm soft tissue volume. *P* refers to comparison of arms by Student's paired *t* test.

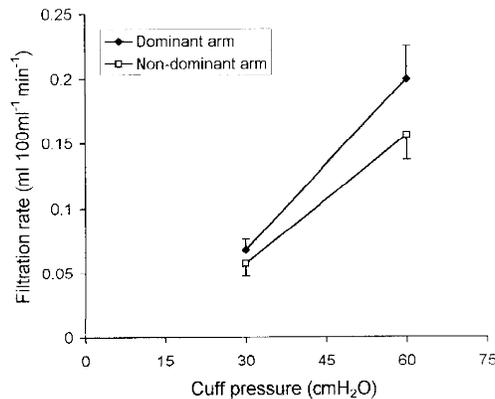


Fig. 4. Filtration rates (FR) in the arms of healthy subjects. Filtration rates per 100 ml forearm soft tissue in the dominant and non-dominant arms (mean ± S.E.M., *n* = 13) are plotted against congestion pressure. The slope represents the filtration capacity of 100 ml soft tissue. The differences between the arms are not statistically significant (Student's paired *t* test; see Table 2 for *P* values).

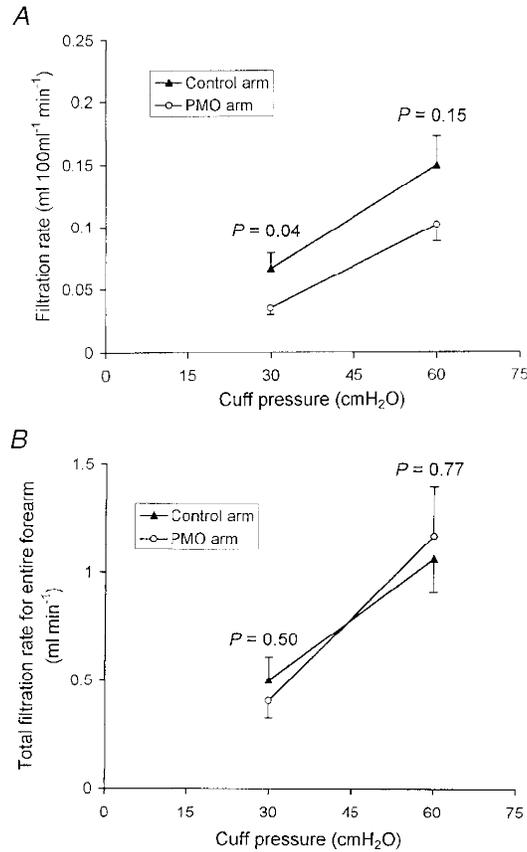


Fig. 5. Filtration rates (FR) in the arms of patients with unilateral postmastectomy oedema (PMO). *A*, filtration rates per 100 ml soft tissue in the PMO and the opposite, unaffected (control) arms (mean \pm S.E.M., $n = 11$) are plotted against congestion pressure. The slope represents filtration capacity per 100 ml tissue. *P* values refer to comparison of filtration rates in the two arms by Student's paired *t* test. *B*, total fluid load on the lymphatic system, calculated as total forearm tissue volume \times filtration rate per ml tissue. Differences between the PMO and control arms are not significant.

7.9 ± 6.9 cmH₂O for the arm with PMO (mean \pm S.E.M.). Again, these values did not differ significantly ($P = 0.77$). Filtration capacity per 100 ml (CFC_a) was similar in the two arms (Table 2). The trend to a lower mean CFC_a in the control arms of patients than in the healthy group did not reach statistical significance ($P = 0.16$, unpaired *t* test).

Since the volume of the arm with PMO was much greater than that of the control arm, the FR was scaled up by total soft tissue volume to calculate the *total* fluid load on the lymphatic system in each forearm (Fig. 5*B*). Total fluid loads are given in Table 2. There were no significant differences between the two arms. Similarly, the filtration capacity of the entire affected forearm, $(25.4 \pm 6.2) \times 10^{-3}$ ml cmH₂O⁻¹ min⁻¹, was not significantly different from that of the control forearm, $(18.3 \pm 2.6) \times 10^{-3}$ ml cmH₂O⁻¹ min⁻¹ ($P = 0.40$).

The lower forearm is subjected to a gravity-induced venous pressure of 30 cmH₂O or more during orthostasis with the arm in a hanging position. In the supine position the arm is usually close to heart level and antecubital venous pressure at heart level is ~ 8 –10 mmHg. Linear

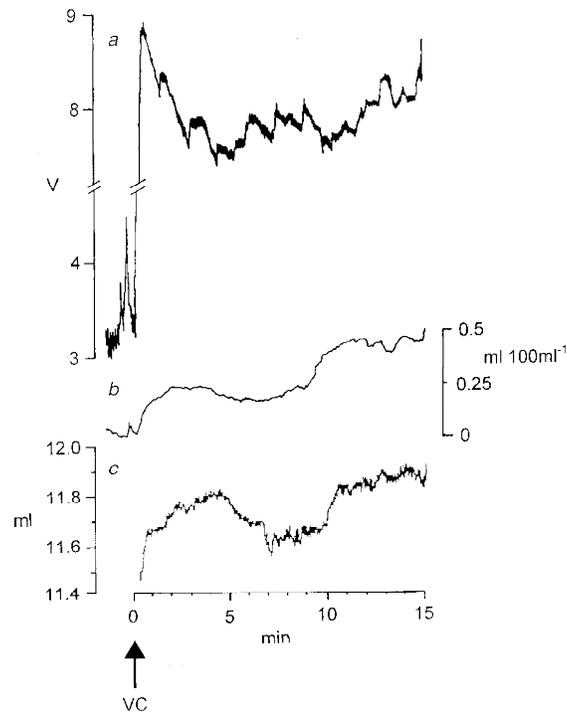


Fig. 6. Photoplethysmograph (PPG) record in a patient with marked oscillations in the swelling records. Simultaneous PPG (trace *a*, in volts, V), mercury strain gauge (trace *b*), and Perometer (trace *c*) recordings over 15 min from a forearm with postmastectomy oedema, following venous congestion (VC) to 30 cmH₂O at time zero. Pronounced, slow undulations are superimposed on the upward incline of the swelling records (traces *b* and *c*). (The original Perometer recording has a different horizontal scale to that of the PPG and the strain gauge but has been expanded to show correspondence with the other records.) The PPG signal peaked rapidly after cuff inflation, then declined before gradually increasing again, with subsidiary oscillations. It does not closely mirror the circumference traces, except on initial congestion, probably because the PPG recording is from a small region of skin, whereas the circumference record is greatly influenced by muscle, the predominant tissue.

extrapolation of the relations in Fig. 5B to venous pressures at heart level indicated that the total filtration load on the lymphatic system of the affected arm in the supine position is no greater than in the opposite, unaffected arm.

Photoplethysmography

To assess whether the phenomenon of volume fluctuations might be of vascular origin, PPG recordings were made in both arms of five patients. Figure 6 shows a PPG recording plus the simultaneous Perometer and strain gauge recordings. The PPG signal rose abruptly as venous congestion increased the local vascular volume. The signal then fell below its initial peak despite the maintained venous congestion pressure. A small dip in the strain gauge record of arm circumference, coinciding with the early dip in the PPG record, was seen in 5/10 arms (not illustrated). The PPG signal then tended to oscillate markedly with a slight general upward trend. The upward trend may reflect the accumulation of haemoconcentrated blood in the capacitance vessels but the oscillations, often rapid, were suggestive of variations in vascular tone.

DISCUSSION

Methodology

The Perometer and mercury strain gauge yielded similar mean results, allaying the initial fear that the mercury loop might sink into oedematous tissues, resulting in underestimation of swelling rates. Differences in results by the two methods in a given arm occurred in either direction, without systematic bias. The mean result for the microvascular filtration capacity of soft tissue in young, healthy subjects, namely $3.8 \times 10^{-3} \text{ ml (100 ml)}^{-1} \text{ cmH}_2\text{O}^{-1} \text{ min}^{-1}$, was similar to literature values, e.g. $3.3 \times 10^{-3} \text{ ml (100 ml)}^{-1} \text{ cmH}_2\text{O}^{-1} \text{ min}^{-1}$ (soft tissue and bone: Landis & Gibbon, 1933), and $3.4 \times 10^{-3} \text{ ml (100 ml)}^{-1} \text{ cmH}_2\text{O}^{-1} \text{ min}^{-1}$ (soft tissue only: Michel & Moyses, 1985). Filtration capacity measured per 100 ml forearm tissue including bone slightly underestimates the value for soft tissue alone.

Volume fluctuations often lead to rejection of swelling rate records, and have been attributed to slight limb movements (Gamble *et al.* 1993) and fluctuating vasomotor tone (Krogh *et al.* 1932). In our subjects sudden shifts in the record were sometimes clearly linked to an observed movement, e.g. talking and myoclonic jerks. Slight longitudinal displacement of the arm within the Perometer frame occurring with some subjects over the long recording period appeared to be the cause of the greater failure rate with this technique in the patient group; the strain gauge by contrast is attached to the skin and is not prone to this form of interference. Less abrupt fluctuations in the swelling record, including a downward slope over many minutes during some Perometer and strain gauge records (Fig. 6), were attributed to changes in whole-limb blood volume, mediated by changes in vascular tone. The PPG recordings provided indirect evidence for fluctuations in vascular volume and tone in small regions of skin. Such changes would have to be co-ordinated over large regions of skin and muscle to affect the circumference record. The skeletal muscle vascular bed and contractions of an obstructed lymphatic system are further possible sources of volume changes. Periodic changes in leg volume ('volumotion') with frequencies of 1–20 cycles min^{-1} have been reported by Christ *et al.* (1995) and attributed to arteriolar vasomotion. Olszewski & Engeset (1980) recorded the frequency of lymphatic contractions in obstructed subcutaneous lymphatic vessels in the human leg and obtained a range of 2.5–10 cycles min^{-1} , also faster than observed in the present study.

Filtration in postmastectomy oedema

Microvascular filtration rate per 100 ml tissue during venous congestion was lower in the arm with PMO than in the unaffected arm. Two mechanisms which could account for this are (i) increased content of water and fibrous tissue per 100 ml oedematous tissue, which reduces or 'dilutes' the density of pre-existing exchange vessels on the PMO side, and (ii) increased opposition to filtration due to changes in the interstitial Starling term, $P_1 - \pi_1$.

The contribution of mechanism (i), microvessel 'dilution', is evident from Fig. 5B, where correction for the increased arm volume brings the congestion filtration rates on the two sides closer together. Dilution of the vasculature in PMO may be inferred from the earlier finding that forearm blood flow per 100 ml tissue is reduced compared with the unaffected arm, but total forearm blood flow is unchanged (Stanton *et al.* 1998). Since the ratio of mean control soft tissue volume to PMO soft tissue volume was 0.62 in the successful studies, simple dilution of pre-existing exchange vessels would, in the absence of angiogenesis or inflammation, reduce the average filtration capacity of 100 ml swollen tissue to 62% of the contralateral value. The observed result was 79%. Because the condition is chronic, angiogenesis may have added

modestly to the original microcirculation, partially compensating for vessel dilation. In support of this, intravital videomicroscopy reveals a small increase in total number of cutaneous capillaries in the PMO forearm (Roberts *et al.* 1994). Increased numbers of capillaries have also been observed in the subcutis in experimentally induced lymphoedema in dogs (Casley-Smith *et al.* 1980). The possibility also exists that the L_p of new capillaries differs from that of the pre-existing vessels (see Introduction), although any difference must be small in view of the observed ΣCFC_a values.

Buffering of filtration by mechanism (ii) (increase in the sum of Starling pressures opposing filtration) is supported by the findings of Bates *et al.* (1994) who measured Starling pressures directly and showed that P_1 is raised in the arm with PMO and that π_1 is reduced. Together these changes increase the opposition to filtration in the affected arms by 6.5–8.8 cmH₂O. In this context the apparent rightward shift of the filtration *versus* pressure relation in the PMO arm is not supported by the similar mean pressure intercepts at zero swelling rate for each arm.

Contribution of results to understanding the pathophysiology of PMO

The study set out to assess filtration rates and filtration capacity in order to discover (a) whether the fluid load on the traumatized lymphatic drainage system was raised or unchanged or reduced, and (b) whether the curious finding of reduced interstitial protein concentration and colloid osmotic pressure in this condition might be explained by increased microvascular filtration rates (Bates *et al.* 1993, 1994).

With regard to (a), the total fluid load from the forearm on the lymphatic drainage system was not significantly different from that in the control arm at a venous congestion pressure of 30 cmH₂O, such as occurs in a dependent arm (Levick & Michel, 1978). Linear extrapolation of the results indicates that in the supine position, where venous pressure in the arm is 8–10 mmHg, the total filtration rate was no greater on the PMO side than on the control side, and may indeed be smaller (see above for discussion of reasons). Since filtration rate is matched by lymph flow in a steady state, the results are consistent with the common assumption that lymph flow in the arm is reduced in PMO in the supine position (for review, see Stanton *et al.* 1996a). Direct measurements of lymph flow in absolute units do not exist.

With regard to (b), the present results argue against increased microvascular filtration as the cause of reduced protein concentration in interstitial fluid in PMO (see Introduction). A study of the mechanisms regulating precapillary vascular tone in the skin in PMO (myogenic response, reactive hyperaemia, neural vasoconstriction and vasodilatation; Stanton *et al.* 1996b) revealed no significant abnormality. The regulation of skeletal muscle blood flow has not been studied in PMO, although the muscle compartment is apparently unaffected by oedema. A study of forearm blood flow in PMO using VOP (Stanton *et al.* 1998) also revealed no evidence for a haemodynamic abnormality. The results of the latter study contrasted with previous reports of hyperaemia in arms with PMO (Jacobsson, 1967; Svensson *et al.* 1994), which triggered the investigations of haemodynamic involvement. The remaining possible explanations for reduced interstitial protein concentration in PMO include, in principle, (i) reduced microvascular permeability to plasma proteins, and (ii) interstitial proteolysis (Casley-Smith, 1983).

To summarize, the weight of evidence indicates that the total filtration load on the lymphatic system in the arm is not increased in PMO, and may even be reduced.

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